Activity of EGFR Tyrosine Kinase Inhibitors in NSCLC With Refractory Leptomeningeal Metastases

ORIGINAL ARTICLE

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ABSTRACT

Introduction: Leptomeningeal metastases (LMs) are associated with dismal prognosis in NSCLC. Optimal management remains unknown in patients with *EGFR*-mutated NSCLC after initial tyrosine kinase inhibitor (TKI) failure.

Methods: We conducted a multicenter retrospective study including patients with *EGFR*-mutated NSCLC and LM. TKI

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failure was defined as diagnosis of LM on TKI, or progression of known LM on TKI.

Results: Ninety-two patients were included, median age of 60 years, predominantly female (68%), never-smokers (74%). *EGFR* mutations included *L858R* (45%), exon *19* deletions (28%), or other mutations (14%). Median time to LM diagnosis was 18.5 months after initial diagnosis of advanced NSCLC. LM was diagnosed after a median of 2 (range: 0–9) systemic therapies. Median overall survival from LM diagnosis was 6.1 months (95% confidence interval [CI]: 4.2–7.6 months). Among 87 patients with TKI failure, patients rechallenged with TKI (n = 50) had a median LM overall survival of 7.6 months (95% CI: 5.7–10.9) compared to 4.2 months (95% CI: 1.6–6.7) in patients without further therapy. Overall, 60% of patients rechallenged with TKI experienced clinical benefit (clinical response or stable disease >2 months), and 23% were treatment failure-free at 6 months. Clinical benefit was reported in 11 of 20 (55%) patients treated with erlotinib after afatinib or gefitinib. Strategies based on increasing dose intensity (n = 17) yielded clinical benefit in 59% of patients. All four patients who received osimertinib after first- and second-generation TKI experienced clinical benefit.

Conclusions: TKI rechallenge strategies, including dosing intensification, may improve clinical outcomes of patients with LM from *EGFR*-mutated NSCLC after initial TKI failure.

Keywords: NSCLC; EGFR; Tyrosine kinase inhibitor; Leptomeningeal metastases

Introduction

Lung cancer is the leading cause of death from cancer worldwide.[1] Targeted molecular therapies provided significant improvements in outcomes of patients presenting with somatic *EGFR* mutations, found in up to 15% of NSCLC cases in the western world.[2] Although underdiagnosed, leptomeningeal metastases (LM) will arise in ∼10% of patients with *EGFR*-mutated NSCLC, leading to dismal outcomes: survival in this population does not exceed 1 year in the era of EGFR-directed tyrosine kinase inhibitors (TKIs).[3,4]

Activity of TKIs in *EGFR*-mutated patients with LM has been only described in relatively small retrospective studies and phase I trials. In addition, cerebrospinal fluid (CSF) penetration may vary for each drug type and dosing.[5,6] In a retrospective study of 21 patients, 48% had cytologic responses to standard dose erlotinib, whereas higher-dose regimens have shown potential to rescue subsets of patients refractory to standard dose therapy.[7-9] High-dose osimertinib (160 mg) has been studied in a phase I study and provided clinical stability or improvement at 12 weeks in 23 of 32 (72%) patients.[10] Likewise, novel EGFR TKIs with high capability to penetrate the blood brain barrier, such as AZD3759, have reported clinical activity in *EGFR*-mutant patients with LM.[11] Nowadays, several EGFR-TKIs are available in EGFR-mutant NSCLC, and optimal therapeutic sequence in this population remains unknown. As LMs often develop during systemic TKI therapy, exploring the activity of subsequent TKI therapy after initial TKI failure is essential.

Herein, we report a joint international effort to evaluate the activity of EGFR-directed TKIs in a large cohort of *EGFR*-mutated NSCLC patients with LM after first TKI failure.

Material and Methods

Patients

We included consecutive patients with *EGFR*-mutated NSCLC and LM across five European institutions: Gustave Roussy, Villejuif, France; Centre Francois Baclesse, Caen, France; Lille University Hospital, Lille, France; Strasbourg University Hospital, Strasbourg, France; and Maastricht UMC+, Maastricht, Netherlands. We collected clinical characteristics of patients as well as disease-related features including imaging, histology, and molecular profiling. Diagnosis of LM was assessed either by cytology of the CSF (European Association of Neuro-Oncology [EANO]-European Society for Medical Oncology [ESMO]–confirmed LM), or by concordant clinical and radiologic assessments including at least brain magnetic resonance imaging (MRI) (EANO-ESMO–probable LM).[12] In case of EANO-ESMO–probable LM, MRI was to be performed before any lumbar puncture to avoid nonspecific leptomeningeal enhancement. TKI failure was defined as: (1) diagnosis of LM during systemic therapy with TKI or (2) progression of known LM on treatment with TKI. TKI rechallenge was defined as a new line of TKI after TKI failure, including administration of other TKI, or regimen adaptations such as dosing modifications of combination therapies. We analyzed outcomes according to systemic and central nervous system (CNS)–directed treatments.

Statistical Analysis

We defined LM overall survival (OS) as time from LM diagnosis to death or last follow-up, and TKI OS from TKI rechallenge to death or last follow-up. Time-to-treatment failure (TTF) was defined as time from TKI rechallenge to treatment discontinuation or death. Patients surviving without treatment failure event were censored at date of last visit. Clinical response was

assessed using physician-reported neurologic outcomes. Clinical benefit was defined as clinical response or stable disease confirmed at least 2 months after treatment initiation. Survival analyses were performed using Kaplan-Meier estimates, and reported along with their 95% confidence intervals (95% CIs). A Cox proportional hazards regression model was used to evaluate the association between TKI rechallenge and OS, providing hazard ratio (HR) and 95% CI adjusted for the following characteristics: age; Eastern Cooperative Oncology Group performance status classification at the time of TKI failure; number of lines of therapy before TKI failure; context of TKI failure (diagnosis of LM on TKI, or progression of known LM on TKI). Median follow-up was calculated using the reverse Kaplan Meier method. Statistical analyses have been performed using NCSS 12 (NCSS, LLC) and R Studio.

Results

Patients

Ninety-two patients with *EGFR*-mutated NSCLC and leptomeningeal dissemination were included, diagnosed with LM between August 2003 and October 2018. Median follow-up was 5.6 months (range: 0.1 to 38.6 months). Most patients were female (68%), never-smokers (74%), and had stage IV disease at diagnosis (85%). *EGFR* mutations were determined by gene panel sequencing or polymerase chain reaction–based assays and were predominantly L858R substitutions (45%) or exon 19 deletions (28%). Rare activating *EGFR* mutations were found in 14% of patients, whereas 13% had activating *EGFR* mutations of unspecified subtype. Acquired *T790M* mutations were reported in 15 patients before LM diagnosis.

Median time from initial cancer diagnosis to LM diagnosis was 18.5 months (range 0–106 months). LM was diagnosed after systemic therapy consisting in TKI in 52 of 92 (56%) patients, chemotherapy in 32 of 92 (35%), or before any systemic therapy for stage IV disease in 8 of 92 (9%) patients. Overall, patients received a median number of two systemic therapies (range: 0–9) before diagnosis of LM. Concurrent brain metastases were reported in 61 of 92 (66%) of patients at LM diagnosis, among whom 29 were treated with radiation therapy (Table 1). LM was confirmed by cytology in 63% of patients (EANO-ESMO–confirmed LM), whereas the remaining 37% had typical symptoms and imaging (EANO-ESMO–probable LM). At LM onset, 85 of 92 (92%) patients experienced one or more symptoms related to LM. Most frequent symptoms included headache (26%), cerebellar syndrome (17%), cognitive disorders (21%), and seizures (10%) (Supplementary Table 1).

Table 1. Baseline Characteristics of the Study Population

Baseline Characteristics	N = 92
Median age, (range) y	60 (26-79)
Sex	
Male	29 (32)
Female	63 (68)
Smoking	
Smoker	22 (24)
Nonsmoker	68 (74)
Unknown	2 (2)
Stage at diagnosis	
I	3 (3)
II	1 (1)
III	6 (7)
IV	78 (85)
Unknown	4 (4)
Median number of metastatic sites at diagnosis, (range)	1 (0-5)
EGFR mutation	
Exon 21 L858R	41 (45)
Exon 19 del	26 (28)
Other	13 (14)
Unknown	12 (13)
Median time to LM onset, (range), mo	18.5 (0-106)
LM diagnosis	
Cytology confirmed	58 (63)
Imaging and symptoms	34 (37)
Symptoms related to LM	85 (92)
Concurrent brain metastases	61 (66)
Radiation therapy for brain metastases	
Radiation therapy	29 (32)
Including: WBRT	18 (20)
SRS	8 (9)
WBRT + SRS	3 (3)
No. of systemic treatments before LM diagnosis, median (range)	2 (0-9)

Values are shown as n (%) or median (range).
LM, leptomeningeal metastases.

Overall Survival From LM Diagnosis

Among the entire study population, LM OS was 6.1 months (95% CI: 4.2–7.6), and the 12-month LM OS rate was 27% (95% CI: 18%– 37%) (Fig. 1*A*).

TKI failure occurred in 87 patients: 52 who had LM diagnosis during TKI, and 35 who had progression of known LM after TKI. Five additional patients were not treated with TKI at LM onset and did not receive any further treatment. Overall, 50 of 87 (57%) patients were rechallenged with TKI after TKI failure. Among them, 37 were rechallenged after a diagnosis of LM on TKI, and 13 had known LM that progressed on previous TKI.

LM OS in patients rechallenged with TKI was 7.6 months (95% CI: 5.7–10.9) compared to 4.2 months (95% CI: 1.6–6.7) in patients without any further therapy at TKI failure. The survival benefit was independent from age, Eastern Cooperative Oncology Group performance status, previous lines of therapy, and context of

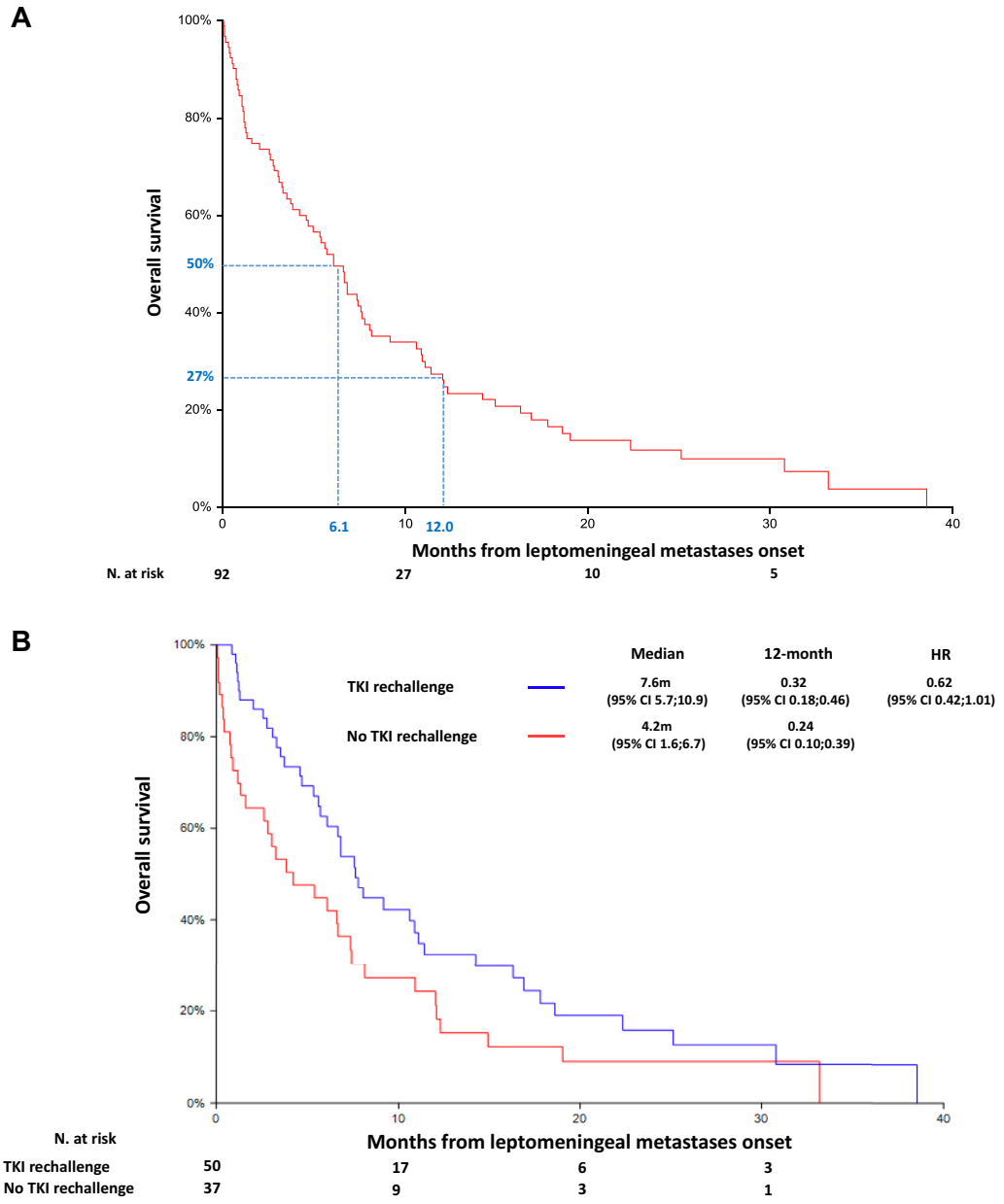

Figure 1. Overall survival in the study population. (*A*) Overall survival from leptomeningeal metastases diagnosis. (*B*) Overall survival according to systemic therapy for refractory leptomeningeal metastases.

TKI failure, with an adjusted HR for death of 0.42 (95% CI: 0.24–0.75) (Supplementary Table 2). Respective 12-month OS rates in both groups were 32% (95% CI: 18%–46%) and 24% (95% CI: 10%–39%) (Fig. 1*B*).

Therapeutic Strategies and Outcomes From TKI Rechallenge

Among 50 patients rechallenged with TKI, 44 (88%) were refractory to first- or second-generation TKI, including erlotinib (19), afatinib (5), or gefitinib (20). Six patients (12%) were refractory to third-generation TKI, including osimertinib (5) and rociletinib (1). Therapeutic sequences after initial TKI failure are detailed in Table 2. Most patients (60%) had TKI switch, whereas 40% were treated with the same TKI but with more intensive regimens, including either dose intensification aiming at increasing CNS diffusion (34%) or combination therapies (6%) (Supplementary Table 3). Patients were treated with a median number of two systemic therapies after initial TKI failure (range: 1–5). Eight patients (16%) received additional intrathecal therapy.

Median TKI OS was 6.8 months (95% CI: 3.7–8.0) across all 50 rechallenged patients. Patients who were rechallenged following LM diagnosis on TKI had longer TKI OS compared to patients rechallenged after

Table 2. Therapeutic Sequence in Patients With TKI Rechallenge at Initial TKI Failure (n = 50)

Treatment	n (%)
Regimen switch	
Erlotinib	22 (44)
From first- / second-generation TKI	20 (40)
From third-generation TKI	2 (4)
Afatinib/gefitinib	4 (8)
From first- / second-generation TKI	4 (8)
Osimertinib	4 (8)
From first-/second-generation TKI	4 (8)
Regimen adaptation	
Increased dose intensity	17 (34)
From first-/second-generation TKI	13 (26)
From third-generation TKI	4 (8)
Combinations	3 (6)
From first-/second-generation TKI	3 (6)
Median no. of systemic therapies after TKI failure (range)	2 (1-5)
Intrathecal therapy for refractory LM	8 (16)

Values are n (%) unless otherwise stated.
TKI, tyrosine kinase inhibitor; LM, leptomeningeal metastases.

progression of known LM on TKI, with respective median TKI OS of 7.8 months (95% CI: 5.7–10.6) and 3.2 months (95% CI: 1.8–4.0), adjusted HR for death 0.42 (95% CI: 0.19–0.92) (Supplementary Table 4).

Median TTF from TKI rechallenge was 2.9 months (95% CI: 2.1–3.7), and 6-month treatment failure–free rate was 23% (95% CI: 11%–35%) (Fig. 2 and Supplementary Fig. 1). No significant difference in median TTF was observed between patients rechallenged after LM diagnosis on TKI and patients rechallenged after progression of known LM on TKI, with respective TTF of 3.3 months (95% CI: 2.1–3.9) and 2.3 months (95% CI: 1.4–3.1).

Forty-nine patients could be evaluated for response to TKI rechallenge. One patient was lost to follow-up immediately after subsequent TKI initiation and therefore not evaluable for response. Clinical response and clinical benefit occurred in 28% and 60% of patients, respectively. Outcomes of patients by treatment subgroups are detailed in Table 3.

Erlotinib was the most frequent TKI used for TKI rechallenge, in 22 of 50 (44%) patients, including 20 patients who had received prior afatinib or gefitinib, and two who had received prior third-generation TKI. Clinical response was observed in 6 of 22 (27%) and clinical benefit in 12 of 22 (54%) patients (Table 3). Median TTF was 2.7 months (95% CI: 1.3–3.7), and 24% of patients were treatment failure–free at 6 months (95% CI: 6%–42%). Of 20 patients who received erlotinib after afatinib or gefitinib failure, 5 (25%) experienced clinical response and 11 (55%) clinical benefit. One clinical response was observed in a patient treated with erlotinib following osimertinib, in a disease without documented T790M mutation.

Seventeen (34%) patients received dose-intensified regimens at TKI rechallenge (Supplementary Table 3). Among those, 6 of 17 (35%) had clinical response and 10 of 17 (59%) clinical benefit. At 6 months, 24% were treatment failure–free (95% CI: 3%–44%). Four patients

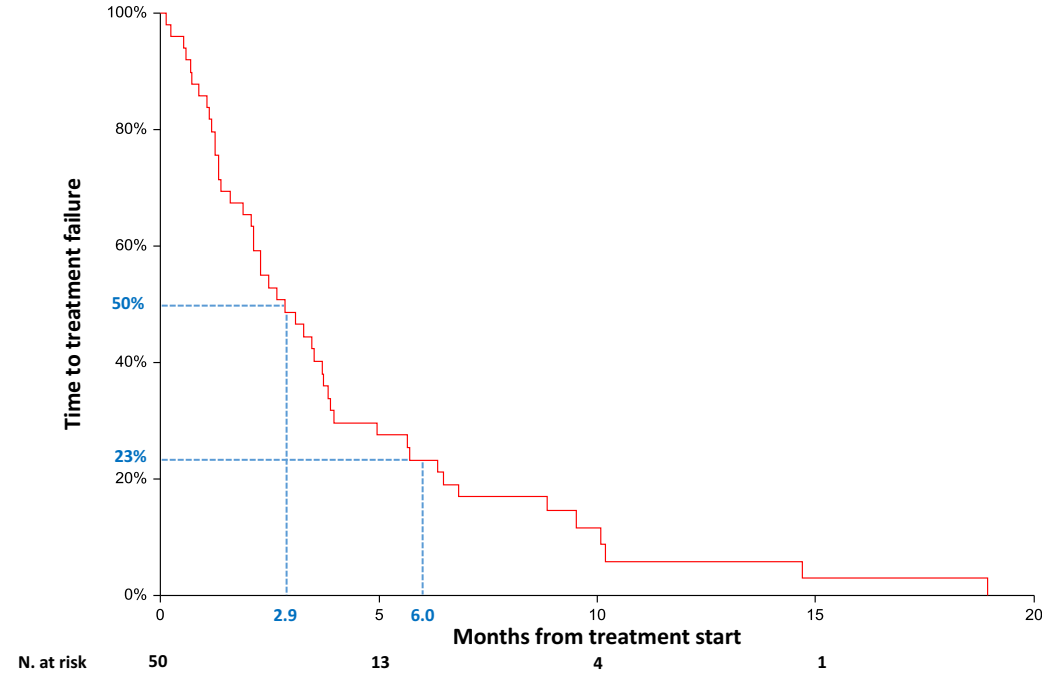

Figure 2. Time-to-treatment failure of patients treated for refractory leptomeningeal metastases.

Table 3. Clinical Response and Time to Treatment Failure According to Therapy for Refractory LM

Variable	Regimen Switch			Regimen Adaptation		
	Erlotinib n = 22	Afatinib / Gefitinib n = 4	Osimertinib n = 4	Increased Dose intensity n = 17	Combinations n = 3	Patients Rechallenged with TKIs n = 50
Clinical response						
Clinical response	6 (27)	1 (25)	1 (25)	6 (35)	0	14 (28)
Stable disease	6 (27)	1 (25)	3 (75)	4 (24)	2 (67)	16 (32)
Progressive disease	9 (41)	2 (50)	0	7 (41)	1 (33)	19 (38)
Unknown	1 (5)	0	0	0	0	1 (2)
Median TTF, months (95% CI)	2.7 (95% CI: 1.3-3.7)	1.1 (95% CI: 0.1-3.5)	10.1 (95% CI: 3.8-14.7)	3.3 (95% CI: 1.9-5.6)	2.3 (95% CI: 1.4-3.7)	2.9 (95% CI: 2.1-3.7)
6-month treatment failure-free rate (95% CI)	24% (95% CI: 6%-42%)	0	67% (95% CI: 13%-100%)	24% (95% CI: 3%-44%)	0	23% (95% CI: 11%-35%)

Values shown are n (%) unless otherwise stated.
TTF, time to treatment failure; LM, leptomeningeal metastases; CI, confidence interval.

with known *T790M* mutations had increased dose intensity from osimertinib-based regimen, leading to clinical benefit for all of them, including three partial responses and one stable disease. Dose modifications were well tolerated. No grade 3/4 toxicities were reported with patients receiving increased dose of first- or second-generation TKIs. Only two patients discontinued osimertinib 160 mg due to grade 3 adverse events including rash and diarrhea.

Four patients switched to osimertinib after first- or second-generation TKI, among whom three had evidence of *T790M* mutation at initial TKI failure. All derived clinical benefit with three having stable diseases and one having clinical response, with prolonged median TTF of 10.1 months. All but one of four patients was alive at the time of the analysis with a median follow-up of 12.6 months after TKI rechallenge.

Patients treated with afatinib or gefitinib after other first- or second-generation TKI had clinical responses in 25% and clinical benefit in 50%, but a short median TTF at 1.1 months (95% CI: 0.1–3.5). No clinical responses were reported in patients treated with combination therapies using the same TKI (n = 3).

Seventeen patients received brain radiation therapy for brain metastases and/or LM before TKI rechallenge, including 13 treated by whole brain radiation therapy. No significant difference in disease control or TTF was observed in this subgroup compared to patients who did not receive radiation therapy, regardless of radiation therapy modality. Additional intrathecal therapy (n = 8) was not associated with improved clinical benefit nor TTF (Supplementary Table 5).

Discussion

This large-scale retrospective study shows that TKI rechallenge provides substantial activity after TKI failure. We observed prolonged LM OS (7.6 versus 4.2 months) in patients who were rechallenged with a TKI, compared to those who were not.

High response rates and prolonged TTF were observed in patients who received erlotinib after first- or second-generation TKI, or who received high-dose erlotinib. These data support the hypothesis that therapeutic resistance in the context of LMs may be related to limited CNS diffusion.[13,14] Erlotinib has better brain-blood-barrier penetration than afatinib or gefitinib, and dose-intensification strategies have been proven to improve CNS diffusion of TKIs.[5,13,15] Prospective studies have confirmed the feasibility of TKI dose increase in clinical practice, notably for erlotinib and osimertinib.[10,16] Thus, current data support the use of rescue high-dose TKI at the time of standard-dose TKI failure in *EGFR*-mutant patients with LM. However, this strategy should be considered only in patients with predominant

CNS disease, as higher-dose therapies may not rescue extracranial resistance after TKI failure.[17]

Although few patients have been treated with third-generation TKI in our cohort, long-term survival has been reported in patients receiving osimertinib including responses that lasted more than 1 year after TKI rechallenge. This is in line with recent reports on intracranial activity of osimertinib for both brain and LMs.[6,10,18,19] Osimertinib may be highly active by targeting diseases which acquire *T790M* mutations, as well as through high CNS concentrations in all-comers. In our study, all patients but one who had TKI rechallenge with osimertinib had a documented *T790M* mutation. As a consequence, we cannot generate data on the LM control by osimertinib used upfront in patients who are *T790M*-negative compared to a sequential strategy. Dedicated studies will be essential to assess the activity of osimertinib in this population as this compound may significantly improve outcomes in this population.

Recent insights into LM biology might help elaborate better therapeutic strategies for these patients. LMs might have different molecular alterations compared to solid brain metastases. In particular, LMs have been found to be enriched in *EGFR,* MET proto-oncogene, receptor tyrosine kinase (*MET*), and tumor protein p53 (*TP53*) mutations, whereas they rarely harbor *KRAS* alterations compared to other solid metastases from NSCLC.[20-22] Tailoring therapy to molecular alterations found in the CSF has been reported to be feasible while providing clinical benefit in subsets of patients.[22] In this context, the use of CSF as liquid biopsy specimens may facilitate translational research programs and help to personalize subsequent treatment.[21]

The choice of clinical endpoints in our study shows the difficulties encountered when assessing response of LMs. MRI evaluation leads to false-negative assessments in up to 30% of patients at diagnosis, whereas sensitivity of cytology can be as low as 50%.[23] Follow-up is equally difficult with the lack of specific evaluation criteria and high variability. At present, clinical outcomes remain a key variable for the evaluation of LMs, considering the high proportion of patients who experience neurologic symptoms and the fact that therapeutic decisions were guided by clinical outcomes in our cohort. The Response Assessment in Neuro-Oncology and EANO-ESMO working groups established frameworks relying on neurologic evaluation, MRI of the CNS, and cytology of the CSF to assess LM diagnosis and follow-up, which may help improve clinical management and drug development in this particular population.[12,24]

In conclusion, our study shows that a strategy using various lines of EGFR TKIs leads to a significant OS benefit in patients with LMs. Regimen switch or strategies using higher dosing may help overcome resistance to TKI in a context of CNS dissemination and improve outcomes. Evaluation of osimertinib in patients with *EGFR*-mutated LMs regardless of T790M status is warranted and could challenge standard of care in this population. Standardized leptomeningeal assessments and translational research programs are needed to better understand resistance mechanisms and improve current therapeutic strategies.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.05.007.

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